HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRINTELLIX safely and effectively. See full prescribing information for TRINTELLIX.

TRINTELLIX (vortioxetine) tablets, for oral use
Initial U.S. Approval: 2013

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants (5.1).**
- **Monitor for worsening and emergence of suicidal thoughts and behaviors (5.1).**
- **TRINTELLIX has not been evaluated for use in pediatric patients (8.4).**

----------INDICATIONS AND USAGE----------
TRINTELLIX is indicated for the treatment of major depressive disorder (MDD) (1, 14).

----------DOSAGE AND ADMINISTRATION----------
- The recommended starting dose is 10 mg administered orally once daily without regard to meals (2.1).
- The dose should then be increased to 20 mg/day, as tolerated (2.1).
- Consider 5 mg/day for patients who do not tolerate higher doses (2.1).
- TRINTELLIX can be discontinued abruptly. However, it is recommended that doses of 15 mg/day or 20 mg/day be reduced to 10 mg/day for one week prior to full discontinuation if possible (2.3).
- The maximum recommended dose is 10 mg/day in known CYP2D6 poor metabolizers (2.6).

----------DOSAGE FORMS AND STRENGTHS----------
TRINTELLIX is available as 5 mg, 10 mg, 15 mg, and 20 mg immediate release tablets (3).

----------CONTRAINDICATIONS----------
- Hypersensitivity to vortioxetine or any components of the TRINTELLIX formulation (4).
- Monoamine Oxidase Inhibitors (MAOIs): Do not use MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX. Do not use TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders. In addition, do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue (4).

----------WARNINGS AND PRECAUTIONS----------
- Serotonin Syndrome has been reported with serotonergic antidepressants (SSRIs, SNRIs, and others), including with TRINTELLIX, both when taken alone, but especially when co-administered with other serotonergic agents (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort). If such symptoms occur, discontinue TRINTELLIX and initiate supportive treatment. If concomitant use of TRINTELLIX with other serotonergic drugs is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases (5.2).
- Treatment with serotonergic antidepressants (SSRIs, SNRIs, and others) may increase the risk of abnormal bleeding. Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, or other drugs that affect coagulation (5.3).
- Activation of Mania/Hypomania can occur with antidepressant treatment. Screen patients for bipolar disorder (5.4).
- Angle Closure Glaucoma: Angle closure glaucoma has occurred in patients with untreated anatomically narrow angles treated with antidepressants. (5.5)
- Hyponatremia can occur in association with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (5.6).

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) were: nausea, constipation and vomiting (6).

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Strong inhibitors of CYP2D6: Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) is coadministered (2.6 and 7.3).
- Strong CYP Inducers: Consider increasing TRINTELLIX dose when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for more than 14 days. The maximum recommended dose should not exceed 3 times the original dose (2.7 and 7.3).

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: Based on animal data, TRINTELLIX may cause fetal harm (8.1).
- Nursing Mothers: Discontinue TRINTELLIX or nursing (8.3).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 9/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a trend toward reduced risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.1)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.1)]*.

TRINTELLIX has not been evaluated for use in pediatric patients *[see Use in Specific Populations (8.4)].*

1 INDICATIONS AND USAGE

1.1 Major Depressive Disorder

TRINTELLIX is indicated for the treatment of major depressive disorder (MDD). The efficacy of TRINTELLIX was established in six 6 to 8 week studies (including one study in the elderly) and one maintenance study in adults *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 General Instruction for Use

The recommended starting dose is 10 mg administered orally once daily without regard to meals. Dosage should then be increased to 20 mg/day, as tolerated, because higher doses demonstrated better treatment effects in trials conducted in the United States. The efficacy and safety of doses above 20 mg/day have not been evaluated in controlled clinical trials. A dose decrease down to 5 mg/day may be considered for patients who do not tolerate higher doses *[see Clinical Studies (14)].*

2.2 Maintenance/Continuation/Extended Treatment

It is generally agreed that acute episodes of major depression should be followed by several months or longer of sustained pharmacologic therapy. A maintenance study of TRINTELLIX demonstrated that TRINTELLIX decreased the risk of recurrence of depressive episodes compared to placebo.

2.3 Discontinuing Treatment

Although TRINTELLIX can be abruptly discontinued, in placebo-controlled trials patients experienced transient adverse reactions such as headache and muscle tension following abrupt discontinuation of TRINTELLIX 15 mg/day or 20 mg/day. To avoid these adverse reactions, it is recommended that the dose be decreased to 10 mg/day for one week before full discontinuation of TRINTELLIX 15 mg/day or 20 mg/day *[see Adverse Reactions (6)]*.

2.4 Switching a Patient To or From a Monoamine Oxidase Inhibitor (MAOI) Intended to Treat Psychiatric Disorders

At least 14 days should elapse between discontinuation of a MAOI intended to treat psychiatric disorders and initiation of therapy with TRINTELLIX to avoid the risk of Serotonin Syndrome *[see Warnings and Precautions (5.2)]*. Conversely, at least 21 days should be allowed after

stopping TRINTELLIX before starting an MAOI intended to treat psychiatric disorders *[see Contraindications (4)].*

2.5 Use of TRINTELLIX with Other MAOIs such as Linezolid or Methylene Blue

Do not start TRINTELLIX in a patient who is being treated with linezolid or intravenous methylene blue because there is an increased risk of serotonin syndrome. In a patient who requires more urgent treatment of a psychiatric condition, other interventions, including hospitalization, should be considered *[see Contraindications (4)].*

In some cases, a patient already receiving TRINTELLIX therapy may require urgent treatment with linezolid or intravenous methylene blue. If acceptable alternatives to linezolid or intravenous methylene blue treatment are not available and the potential benefits of linezolid or intravenous methylene blue treatment are judged to outweigh the risks of serotonin syndrome in a particular patient, TRINTELLIX should be stopped promptly, and linezolid or intravenous methylene blue can be administered. The patient should be monitored for symptoms of serotonin syndrome for 21 days or until 24 hours after the last dose of linezolid or intravenous methylene blue, whichever comes first. Therapy with TRINTELLIX may be resumed 24 hours after the last dose of linezolid or intravenous methylene blue *[see Warnings and Precautions (5.2)].*

The risk of administering methylene blue by non-intravenous routes (such as oral tablets or by local injection) or in intravenous doses much lower than 1 mg/kg with TRINTELLIX is unclear. The clinician should, nevertheless, be aware of the possibility of emergent symptoms of serotonin syndrome with such use *[see Warnings and Precautions (5.2)].*

2.6 Use of TRINTELLIX in Known CYP2D6 Poor Metabolizers or in Patients Taking Strong CYP2D6 Inhibitors

The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 poor metabolizers. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g., bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued *[see Drug Interactions (7.3)]*.

2.7 Use of TRINTELLIX in Patients Taking Strong CYP Inducers

Consider increasing the dose of TRINTELLIX when a strong CYP inducer (e.g., rifampin, carbamazepine, or phenytoin) is coadministered for greater than 14 days. The maximum recommended dose should not exceed three times the original dose. The dose of TRINTELLIX should be reduced to the original level within 14 days, when the inducer is discontinued *[see Drug Interactions (7.3)]*.

3 DOSAGE FORMS AND STRENGTHS

TRINTELLIX is available as immediate-release, film-coated tablets in the following strengths:

- 5 mg: pink, almond shaped biconvex film coated tablet, debossed with “5” on one side and “TL” on the other side
- 10 mg: yellow, almond shaped biconvex film coated tablet, debossed with “10” on one side and “TL” on the other side
- 15 mg: orange, almond shaped biconvex film coated tablet, debossed with “15” on one side and “TL” on the other side
- 20 mg: red, almond shaped biconvex film coated tablet, debossed with “20” on one side and “TL” on the other side

4 CONTRAINDICATIONS

- Hypersensitivity to vortioxetine or any components of the formulation. Angioedema has been reported in patients treated with TRINTELLIX.
- The use of MAOIs intended to treat psychiatric disorders with TRINTELLIX or within 21 days of stopping treatment with TRINTELLIX is contraindicated because of an increased risk of serotonin syndrome. The use of TRINTELLIX within 14 days of stopping an MAOI intended to treat psychiatric disorders is also contraindicated *[see Dosage and Administration (2.4) and Warnings and Precautions (5.2)]*.

  Starting TRINTELLIX in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue is also contraindicated because of an increased risk of serotonin syndrome *[see Dosage and Administration (2.5) and Warnings and Precautions (5.2)].*

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [SSRIs] and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18 to 24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a trend toward reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of two months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in *Table 1*.

Table 1. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	
Increases Compared to Placebo	
<18	14 additional cases
18-24	5 additional cases

Decreases Compared to Placebo	
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.

The following symptoms anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that TRINTELLIX is not approved for use in treating bipolar depression.

5.2 Serotonin Syndrome

The development of a potentially life-threatening serotonin syndrome has been reported with serotonergic antidepressants including TRINTELLIX, when used alone but more often when used concomitantly with other serotonergic drugs (including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's Wort), and with drugs that

impair metabolism of serotonin (in particular, MAOIs, both those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, delirium, and coma), autonomic instability (e.g., tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia), neuromuscular symptoms (e.g., tremor, rigidity, myoclonus, hyperreflexia, incoordination), seizures, and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome.

The concomitant use of TRINTELLIX with MAOIs intended to treat psychiatric disorders is contraindicated. TRINTELLIX should also not be started in a patient who is being treated with MAOIs such as linezolid or intravenous methylene blue. All reports with methylene blue that provided information on the route of administration involved intravenous administration in the dose range of 1 mg/kg to 8 mg/kg. No reports involved the administration of methylene blue by other routes (such as oral tablets or local tissue injection) or at lower doses. There may be circumstances when it is necessary to initiate treatment with a MAOI such as linezolid or intravenous methylene blue in a patient taking TRINTELLIX. TRINTELLIX should be discontinued before initiating treatment with the MAOI *[see Contraindications (4) and Dosage and Administration (2.4)]*.

If concomitant use of TRINTELLIX with other serotonergic drugs, including triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, tryptophan, and St. John's Wort is clinically warranted, patients should be made aware of a potential increased risk for serotonin syndrome, particularly during treatment initiation and dose increases.

Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

5.3 Abnormal Bleeding

The use of drugs that interfere with serotonin reuptake inhibition, including TRINTELLIX, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the increased risk of bleeding when TRINTELLIX is coadministered with NSAIDs, aspirin, or other drugs that affect coagulation or bleeding *[see Drug Interactions (7.2)].*

5.4 Activation of Mania/Hypomania

Symptoms of mania/hypomania were reported in <0.1% of patients treated with TRINTELLIX in pre-marketing clinical studies. Activation of mania/hypomania has been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use TRINTELLIX cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.

5.5 Angle Closure Glaucoma

Angle Closure Glaucoma: The pupillary dilation that occurs following use of many antidepressant drugs, including TRINTELLIX, may trigger an angle closure attack in a patient with anatomically narrow angles who does not have a patent iridectomy.

5.6 Hyponatremia

Hyponatremia has occurred as a result of treatment with serotonergic drugs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). One case with serum sodium lower than 110 mmol/L was reported in a subject treated with TRINTELLIX in a pre-marketing clinical study. Elderly patients may be at greater risk of developing hyponatremia with a serotonergic antidepressant. Also, patients taking diuretics or who are otherwise volume-depleted can be at greater risk. Discontinuation of TRINTELLIX in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. More severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Hypersensitivity *[see Contraindications (4)]*
- Clinical Worsening and Suicide Risk *[see Warnings and Precautions (5.1)]*
- Serotonin Syndrome *[see Warnings and Precautions (5.2)]*
- Abnormal Bleeding *[see Warnings and Precautions (5.3)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.4)]*
- Hyponatremia *[see Warnings and Precautions (5.6)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in clinical practice.

Patient Exposure

TRINTELLIX was evaluated for safety in 4746 patients (18 years to 88 years of age) diagnosed with MDD who participated in pre-marketing clinical studies; 2616 of those patients were exposed to TRINTELLIX in 6 to 8 week, placebo-controlled studies at doses ranging from 5 mg to 20 mg once daily and 204 patients were exposed to TRINTELLIX in a 24 week to 64 week placebo-controlled maintenance study at doses of 5 mg to 10 mg once daily. Patients from the 6 to 8 week studies continued into 12-month open-label studies. A total of 2586 patients were exposed to at least one dose of TRINTELLIX in open-label studies, 1727 were exposed to TRINTELLIX for six months and 885 were exposed for at least one year.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment

In pooled 6 to 8 week placebo-controlled studies the incidence of patients who received TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day and 20 mg/day and discontinued treatment because of an adverse reaction was 5%, 6%, 8% and 8%, respectively, compared to 4% of placebo-treated patients. Nausea was the most common adverse reaction reported as a reason for discontinuation.

Common Adverse Reactions in Placebo-Controlled MDD Studies

The most commonly observed adverse reactions in MDD patients treated with TRINTELLIX in 6 to 8 week placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were nausea, constipation and vomiting.

Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of MDD patients treated with any TRINTELLIX dose and at least 2% more frequently than in placebo-treated patients in the 6 to 8 week placebo-controlled studies.

Table 2. Common Adverse Reactions Occurring in ≥2% of Patients Treated with any TRINTELLIX Dose and at Least 2% Greater than the Incidence in Placebo-treated Patients

System Organ Class Preferred Term	TRINTELLIX 5 mg/day	TRINTELLIX 10 mg/day	TRINTELLIX 15 mg/day	TRINTELLIX 20 mg/day	Placebo
	N=1013 %	N=699 %	N=449 %	N=455 %	N=1621 %
Gastrointestinal disorders					
Nausea	21	26	32	32	9
Diarrhea	7	7	10	7	6
Dry mouth	7	7	6	8	6
Constipation	3	5	6	6	3
Vomiting	3	5	6	6	1
Flatulence	1	3	2	1	1
Nervous system disorders					
Dizziness	6	6	8	9	6
Psychiatric disorders					
Abnormal dreams	<1	<1	2	3	1
Skin and subcutaneous tissue disorders					
Pruritus*	1	2	3	3	1

*includes pruritus generalized

Nausea

Nausea was the most common adverse reaction and its frequency was dose-related *(Table 2)*. It was usually considered mild or moderate in intensity and the median duration was 2 weeks. Nausea was more common in females than males. Nausea most commonly occurred in the first week of TRINTELLIX treatment with 15 to 20% of patients experiencing nausea after 1 to 2 days of treatment. Approximately 10% of patients taking TRINTELLIX 10 mg/day to 20 mg/day had nausea at the end of the 6 to 8 week placebo-controlled studies.

Sexual Dysfunction

Difficulties in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of psychiatric disorders, but they may also be consequences of pharmacologic treatment.

In the MDD 6 to 8 week controlled trials of TRINTELLIX, voluntarily reported adverse reactions related to sexual dysfunction were captured as individual event terms. These event terms have been aggregated and the overall incidence was as follows. In male patients the overall incidence was 3%, 4%, 4%, 5% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to 2% in placebo. In female patients, the overall incidence was <1%, 1%, <1%, 2% in TRINTELLIX 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, respectively, compared to <1% in placebo.

Because voluntarily reported adverse sexual reactions are known to be underreported, in part because patients and physicians may be reluctant to discuss them, the Arizona Sexual Experiences Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in seven placebo-controlled trials. The ASEX scale includes five questions that pertain to the following aspects of sexual function: 1) sex drive, 2) ease of arousal, 3)

ability to achieve erection (men) or lubrication (women), 4) ease of reaching orgasm, and 5) orgasm satisfaction.

The presence or absence of sexual dysfunction among patients entering clinical studies was based on their ASEX scores. For patients without sexual dysfunction at baseline (approximately 1/3 of the population across all treatment groups in each study), *Table 3* shows the incidence of patients that developed treatment-emergent sexual dysfunction when treated with TRINTELLIX or placebo in any fixed dose group. Physicians should routinely inquire about possible sexual side effects.

Table 3. ASEX Incidence of Treatment Emergent Sexual Dysfunction*

	TRINTELLIX 5 mg/day N=65:67†	**TRINTELLIX 10 mg/day** N=94:86†	**TRINTELLIX 15 mg/day** N=57:67†	**TRINTELLIX 20 mg/day** N=67:59†	**Placebo** N=135:162†
Females	22%	23%	33%	34%	20%
Males	16%	20%	19%	29%	14%

*Incidence based on number of subjects with sexual dysfunction during the study / number of subjects without sexual dysfunction at baseline. Sexual dysfunction was defined as a subject scoring any of the following on the ASEX scale at two consecutive visits during the study: 1) total score ≥19; 2) any single item ≥5; 3) three or more items each with a score ≥4

†Sample size for each dose group is the number of patients (females:males) without sexual dysfunction at baseline

Adverse Reactions Following Abrupt Discontinuation of TRINTELLIX Treatment

Discontinuation symptoms have been prospectively evaluated in patients taking TRINTELLIX 10 mg/day, 15 mg/day, and 20 mg/day using the Discontinuation-Emergent Signs and Symptoms (DESS) scale in clinical trials. Some patients experienced discontinuation symptoms such as headache, muscle tension, mood swings, sudden outbursts of anger, dizziness, and runny nose in the first week of abrupt discontinuation of TRINTELLIX 15 mg/day and 20 mg/day.

Laboratory Tests

TRINTELLIX has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (except sodium), hematology and urinalysis as measured in the 6 to 8 week placebo-controlled studies. Hyponatremia has been reported with the treatment of TRINTELLIX *[see Warnings and Precautions (5.6)]*. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12-week, open-label phase, there were no clinically important changes in lab test parameters between TRINTELLIX and placebo-treated patients.

Weight

TRINTELLIX had no significant effect on body weight as measured by the mean change from baseline in the 6 to 8 week placebo-controlled studies. In the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to TRINTELLIX during the initial 12-week, open-label phase, there was no significant effect on body weight between TRINTELLIX and placebo-treated patients.

Vital Signs

TRINTELLIX has not been associated with any clinically significant effects on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies.

Other Adverse Reactions Observed in Clinical Studies
The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Ear and labyrinth disorders — vertigo

Gastrointestinal disorders — dyspepsia

Nervous system disorders — dysgeusia

Vascular disorders — flushing

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of TRINTELLIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Metabolic disorders — weight gain

Gastrointestinal System — acute pancreatitis

7 DRUG INTERACTIONS

7.1 CNS Active Agents

Monoamine Oxidase Inhibitors
Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on a serotonergic antidepressant(s) or who have recently had SSRI or SNRI therapy discontinued prior to initiation of an MAOI *[see Dosage and Administration (2.4), Contraindications (4) and Warnings and Precautions (5.2)]*.

Serotonergic Drugs
Based on the mechanism of action of TRINTELLIX and the potential for serotonin toxicity, serotonin syndrome may occur when TRINTELLIX is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.). Closely monitor symptoms of serotonin syndrome if TRINTELLIX is co-administered with other serotonergic drugs. Treatment with TRINTELLIX and any concomitant serotonergic agents should be discontinued immediately if serotonin syndrome occurs *[see Warnings and Precautions (5.2)].*

Other CNS Active Agents
No clinically relevant effect was observed on steady state lithium exposure following coadministration with multiple daily doses of TRINTELLIX. Multiple doses of TRINTELLIX did not affect the pharmacokinetics or pharmacodynamics (composite cognitive score) of diazepam. A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg) did not increase the impairment of mental and motor skills caused by alcohol (single dose of 0.6 g/kg). Details on the potential pharmacokinetic interactions between TRINTELLIX and bupropion can be found in Section 7.3.

7.2 Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)
Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or

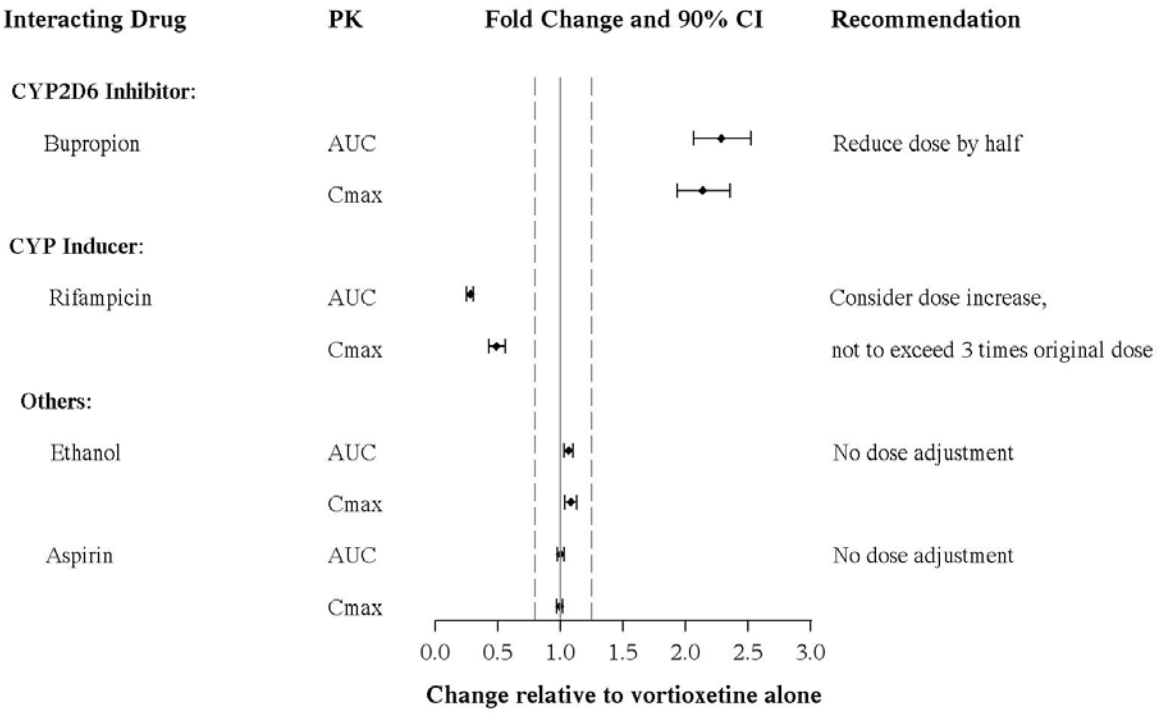
aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin.

Following coadministration of stable doses of warfarin (1 to 10 mg/day) with multiple daily doses of TRINTELLIX, no significant effects were observed in INR, prothrombin values or total warfarin (protein bound plus free drug) pharmacokinetics for both R- and S-warfarin *[see Drug Interactions (7.4)]*. Coadministration of aspirin 150 mg/day with multiple daily doses of TRINTELLIX had no significant inhibitory effect on platelet aggregation or pharmacokinetics of aspirin and salicylic acid *[see Drug Interactions (7.4)]*. Patients receiving other drugs that interfere with hemostasis should be carefully monitored when TRINTELLIX is initiated or discontinued *[see Warnings and Precautions (5.3)].*

7.3 Potential for Other Drugs to Affect TRINTELLIX

Reduce TRINTELLIX dose by half when a strong CYP2D6 inhibitor (e.g., bupropion, fluoxetine, paroxetine, quinidine) is coadministered. Consider increasing the TRINTELLIX dose when a strong CYP inducer (e.g., rifampicin, carbamazepine, phenytoin) is coadministered. The maximum dose is not recommended to exceed three times the original dose *[see Dosage and Administration (2.5 and 2.6)]* (*Figure 1*).

Figure 1. Impact of Other Drugs on Vortioxetine PK



7.4 Potential for TRINTELLIX to Affect Other Drugs

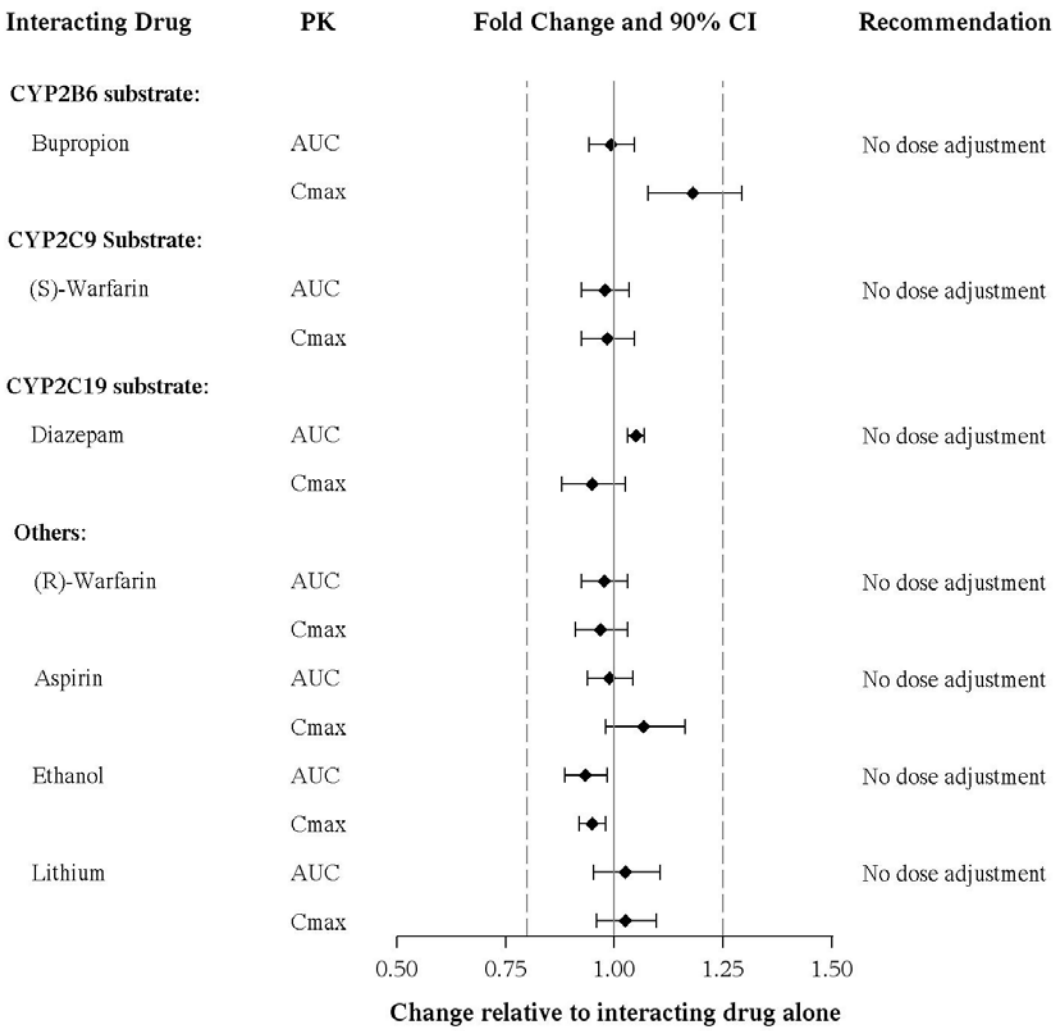
No dose adjustment for the comedications is needed when TRINTELLIX is coadministered with a substrate of CYP1A2 (e.g., duloxetine), CYP2A6, CYP2B6 (e.g., bupropion), CYP2C8 (e.g., repaglinide), CYP2C9 (e.g., S-warfarin), CYP2C19 (e.g., diazepam), CYP2D6 (e.g., venlafaxine), CYP3A4/5 (e.g., budesonide), and P-gp (e.g., digoxin). In addition, no dose adjustment for lithium, aspirin, and warfarin is necessary.

Vortioxetine and its metabolites are unlikely to inhibit the following CYP enzymes and transporter based on *in vitro* data: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, and P-gp. As such, no clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected.

In addition, vortioxetine did not induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of TRINTELLIX is unlikely to induce the metabolism of drugs metabolized by these CYP isoforms. Furthermore, in a series of clinical drug interaction studies, coadministration of TRINTELLIX with substrates for CYP2B6 (e.g., bupropion), CYP2C9 (e.g., warfarin), and CYP2C19 (e.g., diazepam), had no clinical meaningful effect on the pharmacokinetics of these substrates *(Figure 2).*

Because vortioxetine is highly bound to plasma protein, coadministration of TRINTELLIX with another drug that is highly protein bound may increase free concentrations of the other drug. However, in a clinical study with coadministration of TRINTELLIX (10 mg/day) and warfarin (1 mg/day to 10 mg/day), a highly protein-bound drug, no significant change in INR was observed *[see Drug Interactions (7.2)].*

Figure 2. Impact of Vortioxetine on PK of Other Drugs



8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary

There are no adequate and well-controlled studies of TRINTELLIX in pregnant women. Vortioxetine caused developmental delays when administered during pregnancy to rats and

rabbits at doses 15 and 10 times the maximum recommended human dose (MRHD) of 20 mg, respectively. Developmental delays were also seen after birth in rats at doses 20 times the MRHD of vortioxetine given during pregnancy and through lactation. There were no teratogenic effects in rats or rabbits at doses up to 77 and 58 times, the MRHD of vortioxetine, respectively, given during organogenesis. The incidence of malformations in human pregnancies has not been established for TRINTELLIX. All human pregnancies, regardless of drug exposure, have a background rate of 2 to 4% for major malformations, and 15 to 20% for pregnancy loss. TRINTELLIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Neonates exposed to SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of these classes of drugs or possibly, a drug discontinuation syndrome. It should be noted that in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions 5.2]*. When treating a pregnant woman with TRINTELLIX during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Neonates exposed to SSRIs in pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in one to two per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. Several recent epidemiologic studies suggest a positive statistical association between SSRI use in pregnancy and PPHN. Other studies do not show a significant statistical association.

A prospective longitudinal study was conducted of 201 pregnant women with a history of major depression, who were either on antidepressants or had received antidepressants less than 12 weeks prior to their last menstrual period, and were in remission. Women who discontinued antidepressant medication during pregnancy showed a significant increase in relapse of their major depression compared to those women who remained on antidepressant medication throughout pregnancy. When treating a pregnant woman with TRINTELLIX, the physician should carefully consider both the potential risks of taking a serotonergic antidepressant, along with the established benefits of treating depression with an antidepressant.

Animal Data

In pregnant rats and rabbits, no teratogenic effects were seen when vortioxetine was given during the period of organogenesis at oral doses up to 160 and 60 mg/kg/day, respectively. These doses are 77 and 58 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis. Developmental delay, seen as decreased fetal body weight and delayed ossification, occurred in rats and rabbits at doses equal to and greater than 30 and 10 mg/kg (15 and 10 times the MRHD, respectively) in the presence of maternal toxicity (decreased food consumption and decreased body weight gain). When vortioxetine was administered to pregnant rats at oral doses up to 120 mg/kg (58 times the MRHD) throughout pregnancy and lactation, the number of live-born pups was decreased and early postnatal pup mortality was increased at 40 and 120 mg/kg. Additionally, pup weights were decreased at birth to weaning at 120 mg/kg and development (specifically eye opening) was slightly delayed at 40 and 120 mg/kg. These effects were not seen at 10 mg/kg (5 times the MRHD).

8.3 Nursing Mothers

It is not known whether vortioxetine is present in human milk. Vortioxetine is present in the milk of lactating rats. Because many drugs are present in human milk and because of the potential for serious adverse reactions in nursing infants from TRINTELLIX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Clinical studies on the use of TRINTELLIX in pediatric patients have not been conducted; therefore, the safety and effectiveness of TRINTELLIX in the pediatric population have not been established.

8.5 Geriatric Use

No dose adjustment is recommended on the basis of age *(Figure 3)*. Results from a single-dose pharmacokinetic study in elderly (>65 years old) vs. young (24 to 45 years old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups.

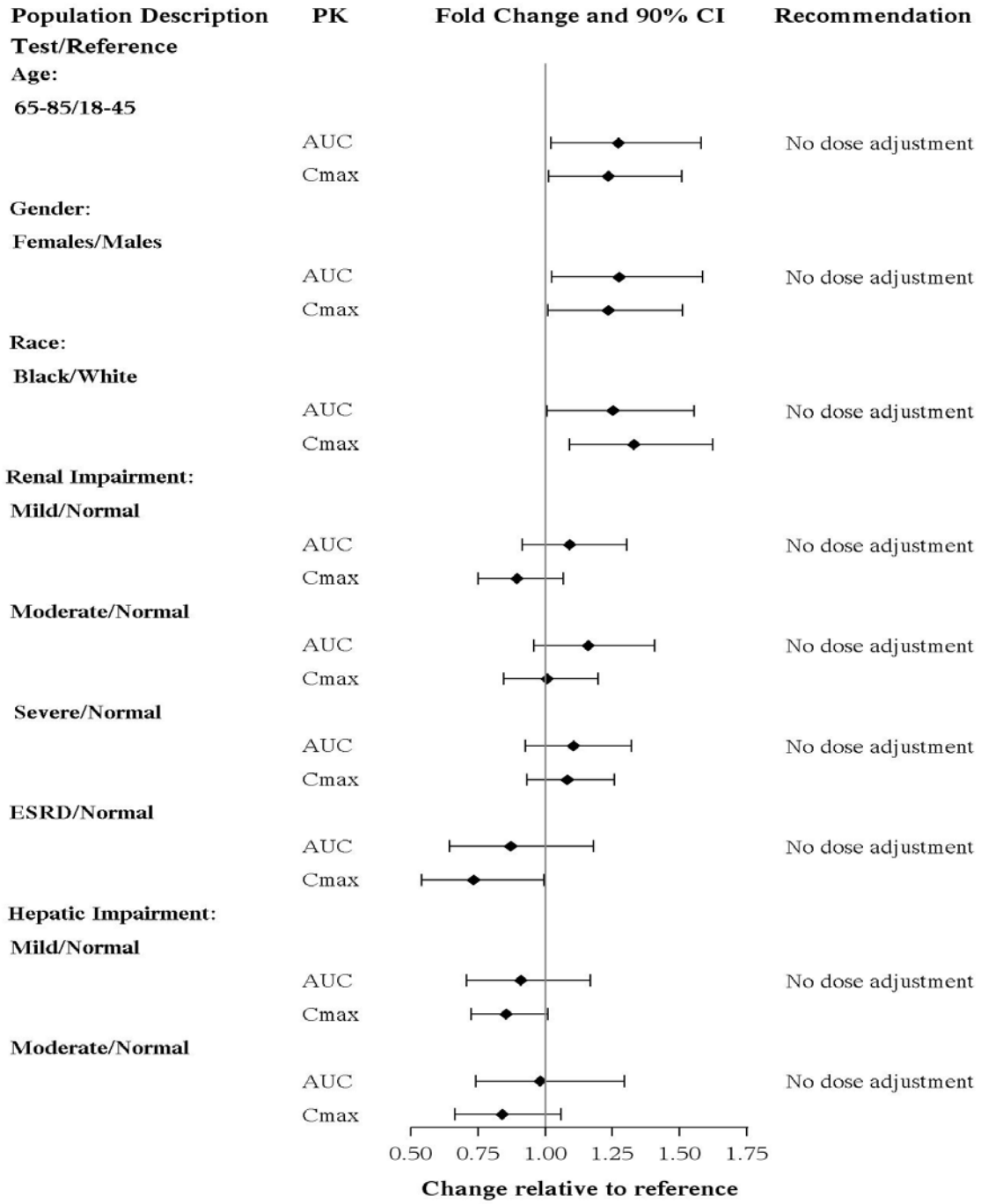
Of the 2616 subjects in clinical studies of TRINTELLIX, 11% (286) were 65 and over, which included subjects from a placebo-controlled study specifically in elderly patients *[see Clinical Studies (14)]*. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions (5.6)].*

8.6 Use in Other Patient Populations

No dose adjustment of TRINTELLIX on the basis of race, gender, ethnicity, or renal function (from mild renal impairment to end-stage renal disease) is necessary. In addition, the same dose can be administered in patients with mild to moderate hepatic impairment *(Figure 3)*. TRINTELLIX has not been studied in patients with severe hepatic impairment. Therefore, TRINTELLIX is not recommended in patients with severe hepatic impairment.

Figure 3. Impact of Intrinsic Factors on Vortioxetine PK



9 DRUG ABUSE AND DEPENDENCE

TRINTELLIX is not a controlled substance.

10 OVERDOSAGE

10.1 Human Experience

There is limited clinical trial experience regarding human overdosage with TRINTELLIX. In pre-marketing clinical studies, cases of overdose were limited to patients who accidentally or intentionally consumed up to a maximum dose of 40 mg of TRINTELLIX. The maximum single dose tested was 75 mg in men. Ingestion of TRINTELLIX in the dose range of 40 to 75 mg was

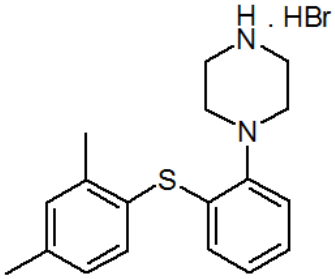
associated with increased rates of nausea, dizziness, diarrhea, abdominal discomfort, generalized pruritus, somnolence, and flushing.

10.2 Management of Overdose

No specific antidotes for TRINTELLIX are known. In managing over dosage, consider the possibility of multiple drug involvement. In case of overdose, call Poison Control Center at 1-800-222-1222 for latest recommendations.

11 DESCRIPTION

TRINTELLIX is an immediate-release tablet for oral administration that contains the beta (β) polymorph of vortioxetine hydrobromide (HBr), an antidepressant. Vortioxetine HBr is known chemically as 1-[2-(2,4-Dimethyl-phenylsulfanyl)-phenyl]-piperazine, hydrobromide. The empirical formula is $C_{18}H_{22}N_2S$, HBr with a molecular weight of 379.36 g/mol. The structural formula is:



Vortioxetine HBr is a white to very slightly beige powder that is slightly soluble in water.

Each TRINTELLIX tablet contains 6.355 mg, 12.71 mg, 19.065 mg, or 25.42 mg of vortioxetine HBr equivalent to 5 mg, 10 mg, 15 mg, or 20 mg of vortioxetine, respectively. The inactive ingredients in TRINTELLIX tablets include mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating which consists of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg, 15 mg, and 20 mg) and iron oxide yellow (10 mg and 15 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of the antidepressant effect of vortioxetine is not fully understood, but is thought to be related to its enhancement of serotonergic activity in the CNS through inhibition of the reuptake of serotonin (5-HT). It also has several other activities including 5-HT3 receptor antagonism and 5-HT1A receptor agonism. The contribution of these activities to vortioxetine's antidepressant effect has not been established.

12.2 Pharmacodynamics

Vortioxetine binds with high affinity to the human serotonin transporter (Ki=1.6 nM), but not to the norepinephrine (Ki=113 nM) or dopamine (Ki>1000 nM) transporters. Vortioxetine potently and selectively inhibits reuptake of serotonin (IC50=5.4 nM). Vortioxetine binds to 5-HT3 (Ki=3.7 nM), 5-HT1A (Ki=15 nM), 5-HT7 (Ki=19 nM), 5-HT1D (Ki=54 nM), and 5-HT1B (Ki=33 nM), receptors and is a 5-HT3, 5-HT1D, and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, and 5-HT1A receptor agonist.

In humans, the mean 5-HT transporter occupancy, based on the results from 2 clinical PET studies using 5-HTT ligands ([^{11}C]-MADAM or [^{11}C]-DASB), was approximately 50% at 5 mg/day, 65% at 10 mg/day and approximately 80% at 20 mg/day in the regions of interest.

Effect on Cardiac Repolarization

The effect of vortioxetine 10 mg and 40 mg administered once daily on QTc interval was evaluated in a randomized, double-blind, placebo-, and active-controlled (moxifloxacin 400 mg), four-treatment-arm parallel study in 340 male subjects. In the study the upper bound of the one-sided 95% confidence interval for the QTc was below 10 ms, the threshold for regulatory concern. The oral dose of 40 mg is sufficient to assess the effect of metabolic inhibition.

Effect on Driving Performance

In a clinical study in healthy subjects, TRINTELLIX did not impair driving performance, or have adverse psychomotor or cognitive effects following single and multiple doses of 10 mg/day. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that TRINTELLIX therapy does not affect their ability to engage in such activities.

12.3 Pharmacokinetics

Vortioxetine pharmacological activity is due to the parent drug. The pharmacokinetics of vortioxetine (2.5 mg to 60 mg) are linear and dose-proportional when vortioxetine is administered once daily. The mean terminal half-life is approximately 66 hours, and steady-state plasma concentrations are typically achieved within two weeks of dosing.

Absorption

The maximal plasma vortioxetine concentration (C_{max}) after dosing is reached within 7 to 11 hours postdose (T_{max}). Steady-state mean C_{max} values were 9, 18, and 33 ng/mL following doses of 5, 10, and 20 mg/day. Absolute bioavailability is 75%. No effect of food on the pharmacokinetics was observed.

Distribution

The apparent volume of distribution of vortioxetine is approximately 2600 L, indicating extensive extravascular distribution. The plasma protein binding of vortioxetine in humans is 98%, independent of plasma concentrations. No apparent difference in the plasma protein binding between healthy subjects and subjects with hepatic (mild, moderate) or renal (mild, moderate, severe, ESRD) impairment is observed.

Metabolism and Elimination

Vortioxetine is extensively metabolized primarily through oxidation via cytochrome P450 isozymes CYP2D6, CYP3A4/5, CYP2C19, CYP2C9, CYP2A6, CYP2C8 and CYP2B6 and subsequent glucuronic acid conjugation. CYP2D6 is the primary enzyme catalyzing the metabolism of vortioxetine to its major, pharmacologically inactive, carboxylic acid metabolite, and poor metabolizers of CYP2D6 have approximately twice the vortioxetine plasma concentration of extensive metabolizers.

Following a single oral dose of [^{14}C]-labeled vortioxetine, approximately 59% and 26% of the administered radioactivity was recovered in the urine and feces, respectively as metabolites. Negligible amounts of unchanged vortioxetine were excreted in the urine up to 48 hours. The presence of hepatic (mild or moderate) or renal impairment (mild, moderate, severe and ESRD) did not affect the apparent clearance of vortioxetine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Carcinogenicity studies were conducted in which CD-1 mice and Wistar rats were given oral doses of vortioxetine up to 50 and 100 mg/kg/day for male and female mice, respectively, and 40 and 80 mg/kg/day for male and female rats, respectively, for 2 years. The doses in the two species were approximately 12, 24, 20, and 39 times, respectively, the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

In rats, the incidence of benign polypoid adenomas of the rectum was statistically significantly increased in females at doses 39 times the MRHD, but not at 15 times the MRHD. These were considered related to inflammation and hyperplasia and possibly caused by an interaction with a vehicle component of the formulation used for the study. The finding did not occur in male rats at 20 times the MRHD.

In mice, vortioxetine was not carcinogenic in males or females at doses up to 12 and 24 times, respectively, the MRHD.

Mutagenicity

Vortioxetine was not genotoxic in the *in vitro* bacterial reverse mutation assay (Ames test), an *in vitro* chromosome aberration assay in cultured human lymphocytes, and an *in vivo* rat bone marrow micronucleus assay.

Impairment of Fertility

Treatment of rats with vortioxetine at doses up to 120 mg/kg/day had no effect on male or female fertility, which is 58 times the maximum recommended human dose (MRHD) of 20 mg on a mg/m^2 basis.

14 CLINICAL STUDIES

The efficacy of TRINTELLIX in treatment for MDD was established in six 6 to 8 week randomized, double-blind, placebo-controlled, fixed-dose studies (including one study in the elderly) and one maintenance study in adult inpatients and outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) criteria for MDD.

Adults (aged 18 years to 75 years)

The efficacy of TRINTELLIX in patients aged 18 years to 75 years was demonstrated in five 6 to 8 week, placebo-controlled studies (Studies 1 to 5 in *Table 4*). In these studies, patients were randomized to TRINTELLIX 5 mg, 10 mg, 15 mg or 20 mg or placebo once daily. For patients who were randomized to TRINTELLIX 15 mg/day or 20 mg/day, the final doses were titrated up from 10 mg/day after the first week.

The primary efficacy measures were the Hamilton Depression Scale (HAMD-24) total score in Study 2 and the Montgomery-Asberg Depression Rating Scale (MADRS) total score in all other studies. In each of these studies, at least one dose group of TRINTELLIX was superior to placebo in improvement of depressive symptoms as measured by mean change from baseline to endpoint visit on the primary efficacy measurement *(see Table 4)*. Subgroup analysis by age, gender or race did not suggest any clear evidence of differential responsiveness. Two studies of the 5 mg dose in the U.S. (not represented in *Table 4*) failed to show effectiveness.

Elderly Study (aged 64 years to 88 years)

The efficacy of TRINTELLIX for the treatment of MDD was also demonstrated in a randomized, double-blind, placebo-controlled, fixed-dose study of TRINTELLIX in elderly patients (aged 64 years to 88 years) with MDD (Study 6 in *Table 4*). Patients meeting the diagnostic criteria for

recurrent MDD with at least one previous major depressive episode before the age of 60 years and without comorbid cognitive impairment (Mini Mental State Examination score <24) received TRINTELLIX 5 mg or placebo.

Table 4. Primary Efficacy Results of 6 Week to 8 Week Clinical Trials

Study No. [Primary Measure]	Treatment Group	Number of Patients	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[†] (95% CI)
Study 1 [MADRS] Non-US Study	TRINTELLIX (5 mg/day)[‡]	108	34.1 (2.6)	-20.4 (1.0)	-5.9 (-8.6, -3.2)
	TRINTELLIX (10 mg/day)[‡]	100	34.0 (2.8)	-20.2 (1.0)	-5.7 (-8.5, -2.9)
	Placebo	105	33.9 (2.7)	-14.5 (1.0)	--
Study 2 [HAMD-24] Non-US Study	TRINTELLIX (5 mg/day)	139	32.2 (5.0)	-15.4 (0.7)	-4.1 (-6.2, -2.1)
	TRINTELLIX (10 mg/day)[‡]	139	33.1 (4.8)	-16.2 (0.8)	-4.9 (-7.0, -2.9)
	Placebo	139	32.7 (4.4)	-11.3 (0.7)	--
Study 3 [MADRS] Non-US Study	TRINTELLIX (15 mg/day) [‡]	149	31.8 (3.4)	-17.2 (0.8)	-5.5 (-7.7, -3.4)
	TRINTELLIX (20 mg/day) [‡]	151	31.2 (3.4)	-18.8 (0.8)	-7.1 (-9.2, -5.0)
	Placebo	158	31.5 (3.6)	-11.7 (0.8)	--
Study 4 [MADRS] US Study	TRINTELLIX (15 mg/day)	145	31.9 (4.1)	-14.3 (0.9)	-1.5 (-3.9, 0.9)
	TRINTELLIX (20 mg/day) [‡]	147	32.0 (4.4)	-15.6 (0.9)	-2.8 (-5.1, -0.4)
	Placebo	153	31.5 (4.2)	-12.8 (0.8)	--
Study 5 [MADRS] US Study	TRINTELLIX (10 mg/day)	154	32.2 (4.5)	-13.0 (0.8)	-2.2 (-4.5, 0.1)
	TRINTELLIX (20 mg/day) [‡]	148	32.5 (4.3)	-14.4 (0.9)	-3.6 (-5.9, -1.4)
	Placebo	155	32.0 (4.0)	-10.8 (0.8)	--
Study 6 (elderly) [HAMD-24] US and Non-US	TRINTELLIX (5 mg/day) [‡]	155	29.2 (5.0)	-13.7 (0.7)	-3.3 (-5.3, -1.3)
	Placebo	145	29.4 (5.1)	-10.3 (0.8)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[†]Difference (drug minus placebo) in least-squares mean change from baseline.
[‡]Doses that are statistically significantly superior to placebo after adjusting for multiplicity.

Time Course of Treatment Response

In the 6 to 8 week placebo-controlled studies, an effect of TRINTELLIX based on the primary efficacy measure was generally observed starting at Week 2 and increased in subsequent weeks with the full antidepressant effect of TRINTELLIX generally not seen until Study Week 4 or later. *Figure 4* depicts time course of response in U.S. based on the primary efficacy measure (MADRS) in Study 5.

Figure 4. Change from Baseline in MADRS Total Score by Study Visit (Week) in Study 5

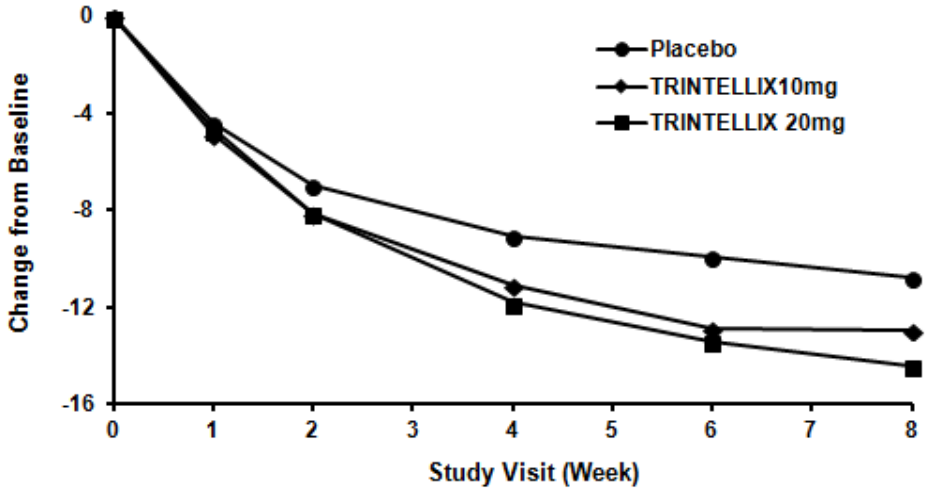
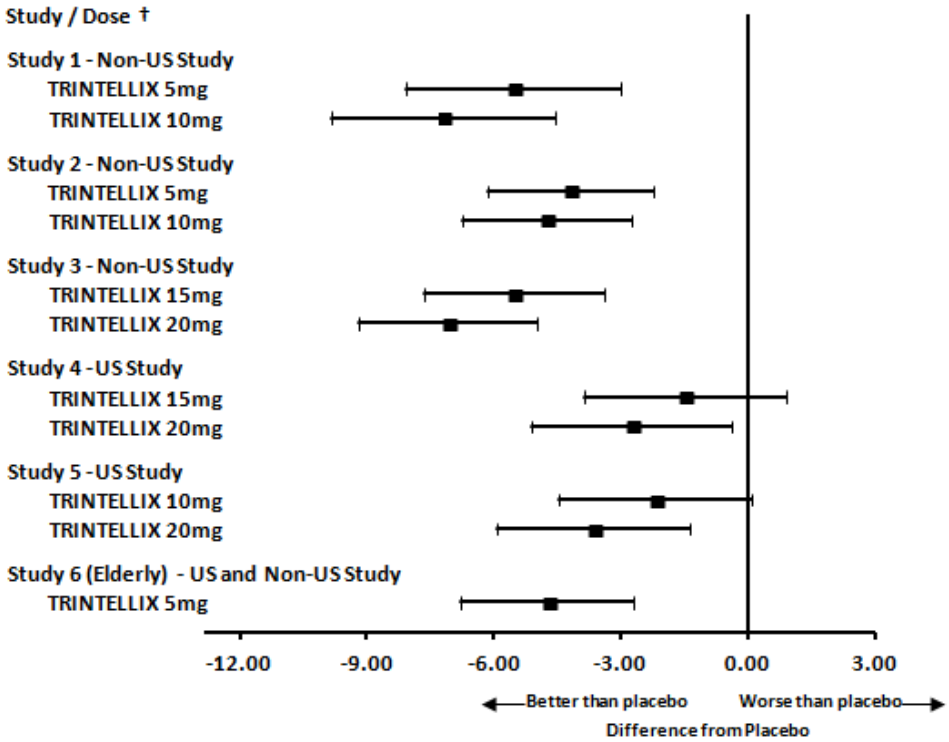


Figure 5. Difference from Placebo in Mean Change from Baseline in MADRS Total Score at Week 6 or Week 8

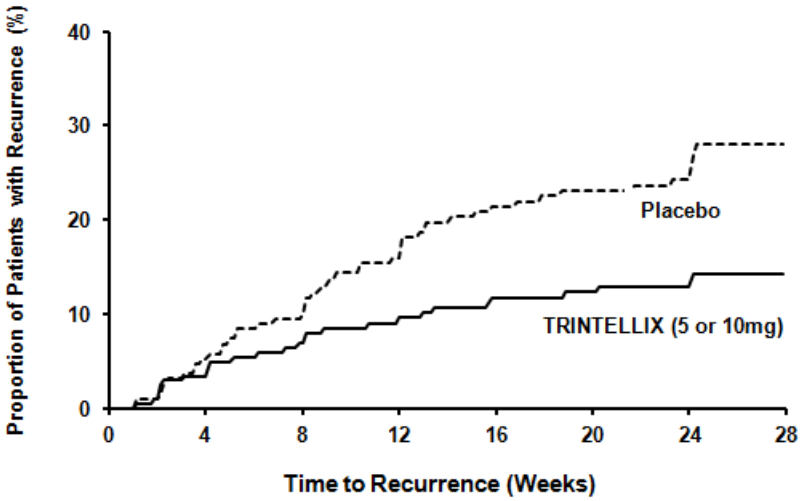


†Results (point estimate and unadjusted 95% confidence interval) are from mixed model for repeated measures (MMRM) analysis. In Studies 1 and 6, the primary analysis was not based on MMRM and in Studies 2 and 6 the primary efficacy measure was not based on MADRS.

Maintenance Study

In a non-US maintenance study (Study 7 in *Figure 6*), 639 patients meeting DSM-IV-TR criteria for MDD received flexible doses of TRINTELLIX (5 mg or 10 mg) once daily during an initial 12 week open-label treatment phase; the dose of TRINTELLIX was fixed during Weeks 8 to 12. Three hundred ninety six (396) patients who were in remission (MADRS total score ≤10 at both Weeks 10 and 12) after open-label treatment were randomly assigned to continuation of a fixed dose of TRINTELLIX at the final dose they responded to (about 75% of patients were on 10 mg/day) during the open-label phase or to placebo for 24 to 64 weeks. Approximately 61% of randomized patients satisfied remission criterion (MADRS total score ≤10) for at least 4 weeks (since Week 8), and 15% for at least 8 weeks (since Week 4). Patients on TRINTELLIX experienced a statistically significantly longer time to have recurrence of depressive episodes than did patients on placebo. Recurrence of depressive episode was defined as a MADRS total score ≥22 or lack of efficacy as judged by the investigator.

Figure 6. Kaplan-Meier Estimates of Proportion of Patients with Recurrence (Study 7)



16 HOW SUPPLIED/STORAGE AND HANDLING

TRINTELLIX tablets are available as follows:

Features	Strengths			
	5 mg	**10 mg**	**15 mg**	**20 mg**
Color	pink	yellow	orange	red
Debossment	"5" on one side of tablet "TL" on other side of tablet	"10" on one side of tablet "TL" on other side of tablet	"15" on one side of tablet "TL" on other side of tablet	"20" on one side of tablet "TL" on other side of tablet
Presentations and NDC Codes				
Bottles of 30	64764-720-30	64764-730-30	64764-740-30	64764-750-30
Bottles of 90	64764-720-90	64764-730-90	64764-740-90	64764-750-90
Bottles of 500	64764-720-77	64764-730-77	64764-740-77	64764-750-77

Storage: Store at 77°F (25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide)

Advise patients and their caregivers about the benefits and risks associated with treatment with TRINTELLIX and counsel them in its appropriate use. Advise patients and their caregivers to read the Medication Guide and assist them in understanding its contents. The complete text of the Medication Guide is reprinted at the end of this document.

Suicide Risk

Advise patients and caregivers to look for the emergence of suicidal ideation and behavior, especially early during treatment and when the dose is adjusted up or down *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Discontinuation of Treatment

Patients who are on TRINTELLIX 15 mg/day or 20 mg/day may experience headache, muscle tension, mood swings, sudden outburst of anger, dizziness and runny nose if they abruptly stop their medicine. Advise patients not stopping TRINTELLIX without talking to their healthcare provider *[see Adverse Reactions (6)]*.

Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter medications because of a potential for interactions. Instruct patients not to take TRINTELLIX with an MAOI or within 14 days of stopping an MAOI and to allow 21 days after stopping TRINTELLIX before starting an MAOI *[see Dosage and Administration (2.4), Contraindications (4), Warnings and Precautions (5.2), and Drug Interactions (7.1)]*.

Serotonin Syndrome

Caution patients about the risk of serotonin syndrome, particularly with the concomitant use of TRINTELLIX and triptans, tricyclic antidepressants, fentanyl, Lithium, tramadol, tryptophan supplements, and St. John's Wort supplements *[see Warnings and Precautions (5.2) and Drug Interactions (7.1, 7.2)]*.

Abnormal Bleeding
Caution patients about the increased risk of abnormal bleeding when TRINTELLIX is given with NSAIDs, aspirin, warfarin, or other drugs that affect coagulation *[see Warnings and Precautions (5.3)]*.

Activation of Mania/Hypomania
Advise patients and their caregivers to look for signs of activation of mania/hypomania *[see Warnings and Precautions (5.4)]*.

Angle Closure Glaucoma
Patients should be advised that taking TRINTELLIX can cause mild pupillary dilation, which in susceptible individuals, can lead to an episode of angle closure glaucoma. Pre-existing glaucoma is almost always open-angle glaucoma because angle closure glaucoma, when diagnosed, can be treated definitively with iridectomy. Open-angle glaucoma is not a risk factor for angle closure glaucoma. Patients may wish to be examined to determine whether they are susceptible to angle closure, and have a prophylactic procedure (e.g., iridectomy), if they are susceptible *[see Warnings and Precautions (5.5)]*.

Hyponatremia
Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking TRINTELLIX *[see Warnings and Precautions (5.6)]*.

Nausea
Advise patients that nausea is the most common adverse reaction, and is dose related. Nausea commonly occurs within the first week of treatment, then decreases in frequency but can persist in some patients.

Alcohol
A clinical study has shown that TRINTELLIX (single dose of 20 or 40 mg/day) did not increase the impairment of mental and motor skills caused by alcohol.

Allergic Reactions
Advise patients to notify their healthcare provider if they develop an allergic reaction such as rash, hives, swelling, or difficulty breathing.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during therapy with TRINTELLIX *[see Use in Specific Populations (8.1)]*.

Nursing Mothers
Advise patients to notify their healthcare provider if they are breast-feeding an infant and would like to continue or start TRINTELLIX *[see Use in Specific Populations (8.3)]*.

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MEDICATION GUIDE

TRINTELLIX [trin'-tel-ix]

(vortioxetine)

Tablets

Read this Medication Guide before you start taking TRINTELLIX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about TRINTELLIX?

TRINTELLIX and other antidepressant medicines may cause serious side effects.

1. **Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, or young adults within the first few months of treatment.**
2. **Depression or other serious mental illnesses are the most important causes of suicidal thoughts or actions**. **Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. **How can I watch for and try to prevent suicidal thoughts and actions?**
   - Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
   - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- attempts to commit suicide
- acting on dangerous impulses
- acting aggressive, being angry or violent
- thoughts about suicide or dying
- new or worse depression
- new or worse anxiety
- feeling agitated, restless, angry or irritable
- trouble sleeping
- an extreme increase in activity or talking (mania)
- other unusual changes in behavior or mood
- panic attacks
- new or worse irritability

What is TRINTELLIX?

TRINTELLIX is a prescription medicine used to treat a certain type of depression called Major Depressive Disorder (MDD).

It is important to talk with your healthcare provider about the risks of treating depression and also the risk of not treating it. You should discuss all treatment choices with your healthcare provider.

- Talk to your healthcare provider if you do not think that your condition is getting better with TRINTELLIX treatment.

Who should not take TRINTELLIX?

Do not take TRINTELLIX if you:

- are allergic to vortioxetine, or any of the ingredients in TRINTELLIX. See the end of this Medication Guide for a complete list of ingredients in TRINTELLIX.
- take a Monoamine Oxidase Inhibitor (MAOI). Ask your healthcare provider or pharmacist if you are not sure if you take an MAOI, including the antibiotic linezolid.
- Do not take an MAOI within 21 days of stopping TRINTELLIX.
- Do not start TRINTELLIX if you stopped taking an MAOI in the last 14 days.

What should I tell my healthcare provider before taking TRINTELLIX?

Tell your healthcare provider if you:

- have liver problems
- have or had seizures or convulsions
- have mania or bipolar disorder (manic depression)
- have low salt (sodium) levels in your blood
- have or had bleeding problems
- drink alcohol
- have any other medical conditions
- are pregnant or plan to become pregnant. It is not known if TRINTELLIX will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TRINTELLIX passes into breast milk. Talk to your healthcare provider about the best way to feed your baby if you take TRINTELLIX.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TRINTELLIX and some medicines may interact with each other, may not work as well, or may cause serious side effects when taken together.

Especially tell your healthcare provider if you take:

- medicines used to treat migraine headache (e.g. triptans)
- medicines used to treat mood, anxiety, psychotic or thought disorders, including tricyclics, lithium, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), buspirone, or antipsychotics
- MAOIs (including linezolid, an antibiotic)
- Tramadol or fentanyl
- over-the-counter supplements such as tryptophan or St. John's Wort
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- aspirin
- warfarin (Coumadin, Jantoven)
- diuretics
- rifampicin
- carbamazepine
- phenytoin
- quinidine

Ask your healthcare provider if you are not sure if you are taking any of these medicines.

Before you take TRINTELLIX with any of these medicines, talk to your healthcare provider about serotonin syndrome. See "What are the possible side effects of TRINTELLIX?"

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get new medicine.

How should I take TRINTELLIX?

- Take TRINTELLIX exactly as your healthcare provider tells you to take it.
- Take TRINTELLIX at about the same time each day.
- Your healthcare provider may need to change the dose of TRINTELLIX until it is the right dose for you.
- Do not start or stop taking TRINTELLIX without talking to your healthcare provider first. Suddenly stopping TRINTELLIX when you take higher doses may cause you to have side effects, including:
  - headache
  - stiff muscles
  - mood swings
  - sudden outburst of anger
  - dizziness or feeling lightheaded
  - runny nose
- TRINTELLIX may be taken with or without food.
- If you take too much TRINTELLIX, call the Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking TRINTELLIX?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how TRINTELLIX affects you.
- Avoid drinking alcohol while taking TRINTELLIX.

What are the possible side effects of TRINTELLIX?

TRINTELLIX may cause serious side effects, including:

- **See "What is the most important information I should know about TRINTELLIX?"**
- **serotonin syndrome.** A potentially life-threatening problem called serotonin syndrome can happen when medicines such as TRINTELLIX are taken with certain other medicines. Symptoms of serotonin syndrome may include:
  - agitation, hallucinations, coma or other changes in mental status
  - problems controlling your movements or muscle twitching
  - fast heartbeat
  - high or low blood pressure
  - sweating or fever
  - nausea or vomiting
  - diarrhea
  - muscle stiffness or tightness
- **abnormal bleeding or bruising.** TRINTELLIX may increase your risk of bleeding or bruising, especially if you take the blood thinner warfarin (Coumadin®, Jantoven®), a non-steroidal anti-inflammatory drug (NSAID), or aspirin.

- **hypomania** (manic episodes). Symptoms of manic episodes include:
  - greatly increased energy
  - severe problems sleeping
  - racing thoughts
  - reckless behavior
  - unusually grand ideas
  - excessive happiness or irritability
  - talking more or faster than usual
- **visual problems**
  - eye pain
  - changes in vision
  - swelling or redness in or around the eye

  Only some people are at risk for these problems. You may want to undergo an eye examination to see if you are at risk and receive preventative treatment if you are.
- **low levels of salt (sodium) in your blood**. Symptoms of this may include: headache, difficulty concentrating, memory changes, confusion, weakness and unsteadiness on your feet. Symptoms of severe or sudden cases of low salt levels in your blood may include: hallucinations (seeing or hearing things that are not real), fainting, seizures and coma. If not treated, severe low sodium levels can cause death.

Common side effects in people who take TRINTELLIX include:

- nausea
- constipation
- vomiting

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of TRINTELLIX. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRINTELLIX?

Store TRINTELLIX at room temperature between 59°F to 86°F (15°C to 30°C).

Keep TRINTELLIX and all medicines out of the reach of children.

General information about the safe and effective use of TRINTELLIX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TRINTELLIX for a condition for which it was not prescribed. Do not give TRINTELLIX to other people, even if they have the same condition. It may harm them.

This Medication Guide summarizes the most important information about TRINTELLIX. If you would like more information, talk with your healthcare provider. You may ask your healthcare provider or pharmacist for information about TRINTELLIX that is written for healthcare professionals.

For more information, go to www.TRINTELLIX.com or call 1-877-TAKEDA-7 (1-877-825-3327).

What are the ingredients in TRINTELLIX?

Active ingredient: vortioxetine hydrobromide

Inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, sodium starch glycolate, magnesium stearate and film coating consisting of hypromellose, titanium dioxide, polyethylene glycol 400, iron oxide red (5 mg, 15 mg, and 20 mg) and iron oxide yellow (10 mg and 15 mg)

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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